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PPAR-α activation by fenofibrate modulates anxiety-like behaviors in a ketamine-induced schizophrenia-like rat model

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ABSTRACT

Introduction: The pathophysiology of schizophrenia involves complex interactions among multiple neural systems, including glutamatergic and dopaminergic neurotransmission, as well as synaptic dysfunction, neuroinflammation, and oxidative disturbances. The current study investigated the effects of fenofibrate, a peroxisome proliferator-activated receptor alpha (PPAR-α) agonist, on anxiety-like behaviors and locomotor activity in a ketamine-induced schizophrenia-like rat model.

Materials and Methods: Twenty-eight male Wistar rats were randomly divided into four groups: control, ketamine-induced schizophrenia, and two schizophrenia groups treated with fenofibrate at doses of 100 and 200 mg/kg/day. Ketamine (30 mg/kg/day) was administered for 10 consecutive days to induce schizophrenia-like model. Subsequently, anxiety-like behaviors and locomotor activity were evaluated using the elevated plus-maze (EPM) test. The percentage of time spent in, and the percentage of entries into, the open and closed arms were recorded as behavioral indices.

Results: Ketamine administration significantly reduced locomotor activity and the percentage of time spent in the open arms, while increasing the percentage of time spent in the closed arms. Treatment with fenofibrate at 100 mg/kg significantly altered EPM time-related indices, with the percentages of time spent in the open and closed arms approaching those observed in the control group. In contrast, fenofibrate at 200 mg/kg exhibited a different pattern, which was similar to that observed in the schizophrenia group.

Conclusion: Fenofibrate treatment partially ameliorated anxiety-like behaviors, suggesting that PPAR-α activation may have a modulatory role in anxiety-related behavioral defects associated with the ketamine-induced schizophrenia-like model.

Keywords: Schizophrenia; Ketamine; Fenofibrate; PPAR-α; Anxiety-like behavior; Locomotor activity.

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Introduction

Evidence from clinical and preclinical studies indicates that schizophrenia arises from the interplay of multiple neurobiological processes, including disrupted glutamatergic and dopaminergic transmission, altered synaptic function and plasticity, imbalances between neuronal excitation and inhibition, neuroinflammation, oxidative stress, and mitochondrial dysfunction (1-3). The interaction among these processes can ultimately impair the functioning of neural circuits involved in cognition, emotion, motivation, and behavior, thereby giving rise to the diverse spectrum of symptoms associated with the disorder (4). Among the mechanisms implicated in the pathophysiology of schizophrenia, dysfunction of the glutamatergic system, particularly altered N-methyl-D-aspartate (NMDA) receptor function, has received particular attention (5). NMDA receptors are key glutamatergic receptors that play fundamental roles in excitatory neurotransmission, synaptic connectivity, neuroplasticity, learning, and information processing (1). Dysfunction of these receptors, particularly on inhibitory GABAergic neurons, can disrupt the balance between neuronal excitation and inhibition within neural networks (5). Such disruption may alter the activity of cortical and limbic circuits and subsequently lead

to secondary changes in the regulation of the dopaminergic system (6). One consequence of dysfunction within these neural networks may be impaired emotional regulation and altered responses to threatening stimuli (2). Anxiety and anxiety-like behaviors are important features investigated in the context of neuropsychiatric disorders (7). The regulation of anxiety-related behavior depends on complex interactions among the amygdala, hippocampus, prefrontal cortex, and other components of the limbic system and is modulated by several neurotransmitter systems, including glutamate, GABA, dopamine, and serotonin (8). Consequently, alterations in glutamatergic and dopaminergic network function, in addition to affecting cognition and schizophrenia-related behaviors, may also influence the regulation of emotional responses and anxiety-like behaviors (7).

The peroxisome proliferator-activated receptor (PPAR) family, a group of ligand-activated nuclear receptors, plays an important role in regulating gene expression, energy metabolism, lipid homeostasis, and inflammatory responses (9). Among these receptors, PPAR-α has attracted considerable neurobiological interest because of its involvement in fatty acid metabolism, mitochondrial function, inflammatory responses, and the regulation of oxidative stress (10). The importance of PPAR-α in the nervous system extends beyond metabolic regulation, as its activation can influence the neuronal environment by modulating pathways associated with inflammation and oxidative stress (11). At the molecular level, PPAR-α interacts with pathways involved in the regulation of pro-inflammatory gene expression and, under certain conditions, can suppress inflammatory activity (12). Furthermore, enhanced metabolic capacity and improved mitochondrial function may contribute to the maintenance of cellular redox homeostasis (9, 13). Consequently, PPAR-α represents a potential mechanistic link among several processes implicated in the pathophysiology of schizophrenia, including neuroinflammation, oxidative stress, dysregulated energy metabolism, and altered synaptic function (13). Within this framework, fenofibrate, a well-established PPAR-α agonist, has emerged as a compound of considerable interest in preclinical research. Although fenofibrate is primarily recognized for its metabolic effects, experimental evidence from various neurological models indicates that PPAR-α activation can modulate inflammatory, oxidative, and metabolic processes (11, 12). Furthermore, animal studies suggest that modulation of the PPAR-α pathway may influence behavioral phenotypes associated with NMDA receptor dysfunction (14, 15). These findings raise the possibility that PPAR-α activation may represent a potential pathway for modulating neurological and behavioral outcomes associated with glutamatergic dysfunction (13).

Given the potential involvement of glutamatergic dysfunction, neuroinflammation, oxidative stress, impaired cellular metabolism, and altered synaptic function in the pathophysiology of schizophrenia, as well as the potential role of PPAR-α in regulating these processes, the present study aimed to investigate the effects of fenofibrate, a PPAR-α agonist, on anxiety-like behaviors and locomotor activity in a ketamine-induced schizophrenia-like rat model.

Materials and Methods

Animals

A total of 28 adult male Wistar rats weighing 180-220 g were obtained from the laboratory animal breeding facility of Baqiyatallah University of Medical Sciences. The animals were housed under standard laboratory conditions at an ambient temperature of 22 ± 1°C with a 12:12-h light/dark cycle and ad libitum access to water and standard laboratory chow.

Experimental Groups

The animals were randomly assigned to four groups, with 7 rats in each group. The first group selected as the control group. These animals were maintained under standard conditions, did not undergo ketamine-induced schizophrenia-like modeling, and received no treatment. The second group, designated as the schizophrenia group, received daily intraperitoneal injections of ketamine at a dose of 30 mg/kg body weight for 10 consecutive days to induce schizophrenia-like model. The third group, designated as the schizophrenia + fenofibrate 100 group, underwent the same ketamine treatment as the second group and received fenofibrate orally at a dose of 100 mg/kg body weight. The fourth group, designated as the schizophrenia + fenofibrate 200 group, underwent the same ketamine treatment as the second and third groups and received fenofibrate orally at a dose of 200 mg/kg body weight.

Induction of the Ketamine-Induced Schizophrenia-Like Model

To induce schizophrenia-like model, ketamine was administered at a dose of 30 mg/kg body weight once daily for 10 consecutive days (16). Ketamine was administered via the intraperitoneal route, and the dose was calculated individually based on each animal's body weight. Animals assigned to the ketamine-treated groups received the drug according to the experimental protocol.

Fenofibrate Administration

Fenofibrate, a PPAR-α agonist, was administered at doses of 100 and 200 mg/kg body weight. The doses of fenofibrate (100 and 200 mg/kg/day) were selected based on our previous studies investigating its neuroprotective effects in experimental animal models. The drug was administered orally once daily to the treatment groups according to the experimental protocol. The required dose was calculated individually based on each animal's body weight. Fenofibrate was prepared in a 0.5% carboxymethyl cellulose (CMC) solution, which selected as the vehicle. The administration volume was set at [volume in mL/kg]. Animals in the control group received the corresponding vehicle at an equivalent administration volume to control for potential effects of the vehicle on behavioral outcomes.

Assessment of Anxiety-Like Behaviors

The elevated plus-maze (EPM) test was used to assess anxiety-like behaviors and general locomotor activity. The EPM is based on the natural conflict between a rodent's exploratory drive and its aversion to elevated and unprotected spaces (17). The EPM apparatus consisted of two open arms and two closed arms arranged in a plus-shaped configuration perpendicular to one another. The apparatus was elevated 60 cm above the floor and maintained under standard lighting and environmental conditions. Walls measuring 40 cm in height were positioned along the closed arms to prevent the animals from falling. At the beginning of the test, each animal was placed in the center of the apparatus with its orientation standardized according to the experimental protocol. The animal was then allowed to explore the maze freely for five minutes. During this period, the number of entries into the open arms and the time spent in the open arms were recorded. Between trials, the apparatus was cleaned according to the predefined experimental protocol to minimize the potential influence of residual odors on the behavior of subsequent animals. Arm entries and the duration spent in each arm were recorded according to predefined behavioral criteria. A full entry into an arm was defined as the entry of all four limbs into that arm, and this criterion was applied consistently across all animals.

Behavioral Variables and Computational Indices

The primary behavioral variables included the percentage of time spent in the open and closed arms, the percentage of entries into the open and closed arms, and the total number of arm entries as an indirect index of locomotor activity. The total number of complete entries into the open and closed arms was used as an indirect behavioral index of general locomotor activity.

The percentage of time spent in the open arms was calculated by dividing the total time spent in the open arms by the total test duration and multiplying the result by 100. An increase in this index may indicate reduced avoidance of open spaces and increased exploratory behavior; however, its interpretation should be considered in conjunction with arm-entry and locomotor activity indices. Similarly, the percentage of time spent in the closed arms was calculated by dividing the total time spent in the closed arms by the total test duration and multiplying the result by 100. An increase in this index may indicate greater preference for protected spaces and increased avoidance of open areas.

The percentage of entries into the open arms was calculated by dividing the number of complete entries into the open arms by the total number of complete entries into both the open and closed arms and multiplying the result by 100. This index represents the proportion of entries into the open arms relative to the total number of recorded entries. Similarly, the percentage of entries into the closed arms was calculated by dividing the number of complete entries into the closed arms by the total number of complete entries into both the open and closed arms and multiplying the result by 100.

Statistical Analysis

Data are presented as mean ± standard error of the mean (SEM). Statistical analyses were performed using SPSS software, version 21.

The normality of data distribution was assessed using the [Shapiro–Wilk/Kolmogorov–Smirnov] test. For normally distributed data, differences among groups were analyzed using one-way analysis of variance (ANOVA), followed by the [Fisher's LSD] post hoc test, as appropriate. A P-value < 0.05 was considered statistically significant. Where applicable, 95% confidence intervals were also calculated.

Results

Effect of Schizophrenia Induction on Locomotor Activity and the Effect of Fenofibrate

As shown in Figure 1, locomotor activity was significantly reduced in the ketamine-induced schizophrenia-like model group compared with the normal control group. Furthermore, locomotor activity remained lower than that of the normal control group in both fenofibrate-treated groups (100 and 200 mg/kg). Thus, fenofibrate treatment at either of the tested doses did not restore locomotor activity to the level observed in the normal control group.

Effect of Schizophrenia Induction on the Percentage of Time Spent in the Open and Closed Arms and the Effect of Fenofibrate

As illustrated in Figure 2, induction of the schizophrenia-like model with ketamine was associated with a decrease in the percentage of time spent in the open arm and an increase in the percentage of time spent in the closed arm. In the group treated with fenofibrate at a dose of 100 mg/kg, the time-related indices of the elevated plus-maze shifted toward the values observed in the normal control group. Specifically, the percentage of time spent in the open arm increased, whereas the percentage of time spent in the closed arm decreased. In contrast, in the schizophrenia-like model group treated with fenofibrate at a dose of 200 mg/kg, the reduction in the percentage of time spent in the open arm and the increase in the percentage of time spent in the closed arm persisted, showing a pattern similar to that observed in the untreated ketamine group.

Effect of Schizophrenia Induction on the Percentage of Entries into the Open and Closed Arms and the Effect of Fenofibrate

The results for the percentage of entries into the open and closed arms of the elevated plus-maze are presented in Figure 3. Unlike the time-related indices, the percentage of arm entries showed more limited variation across the experimental groups and did not follow the same pattern observed for the time spent in the arms. The percentage of entries into the open arm showed minimal variation across the experimental groups, and no statistically significant differences were observed for this index. In contrast, the percentage of entries into the closed arm was significantly increased only in the group treated with fenofibrate at a dose of 200 mg/kg compared with the ketamine group.

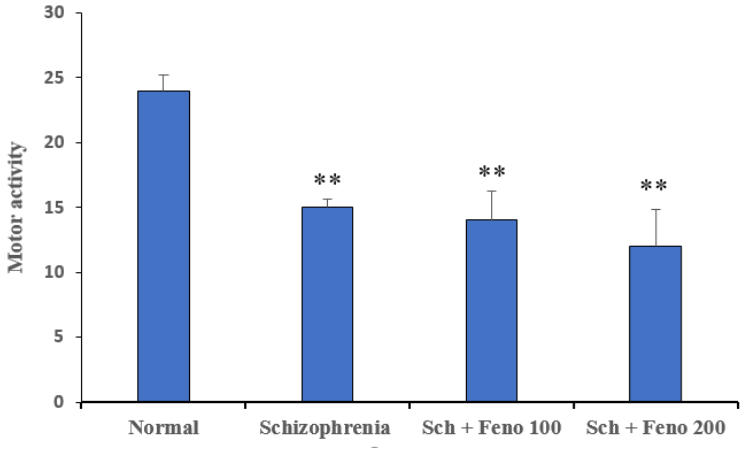


Fig. 1: Effect of fenofibrate on locomotor activity in the elevated plus-maze in a ketamine-induced animal model of schizophrenia. All data are presented as mean ± standard error of the mean (SEM). The symbol ** ($p < 0.01$) indicates a statistically significant difference compared with the normal control group.

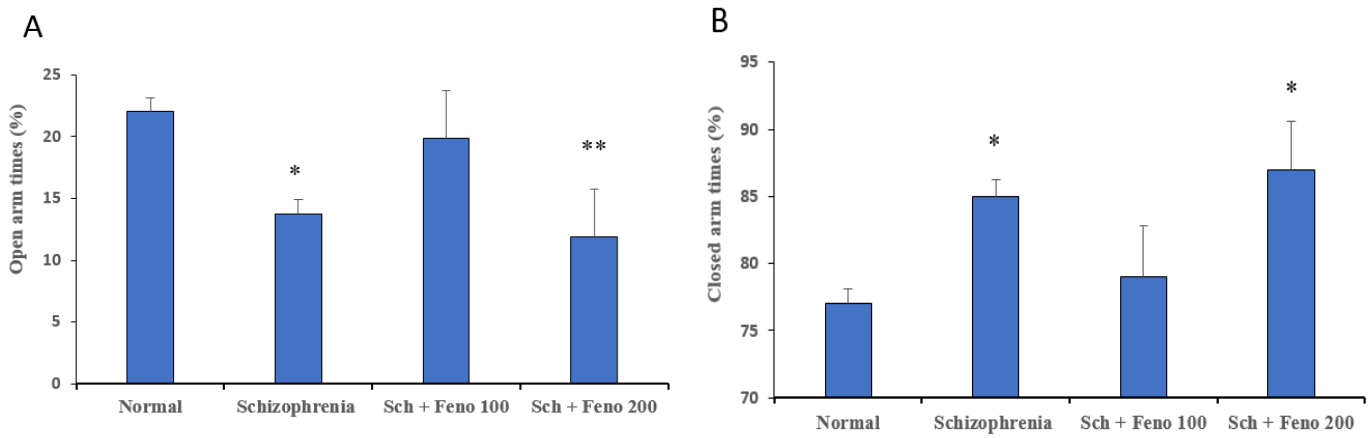


Fig. 2: Effect of fenofibrate on the percentage of time spent in the open arm (A) and closed arm (B) of the elevated plus-maze in a ketamine-induced animal model of schizophrenia. All data are presented as mean ± standard error of the mean (SEM). The symbols * ($p < 0.05$) and ** ($p < 0.01$) indicate statistically significant differences compared with the normal control group.

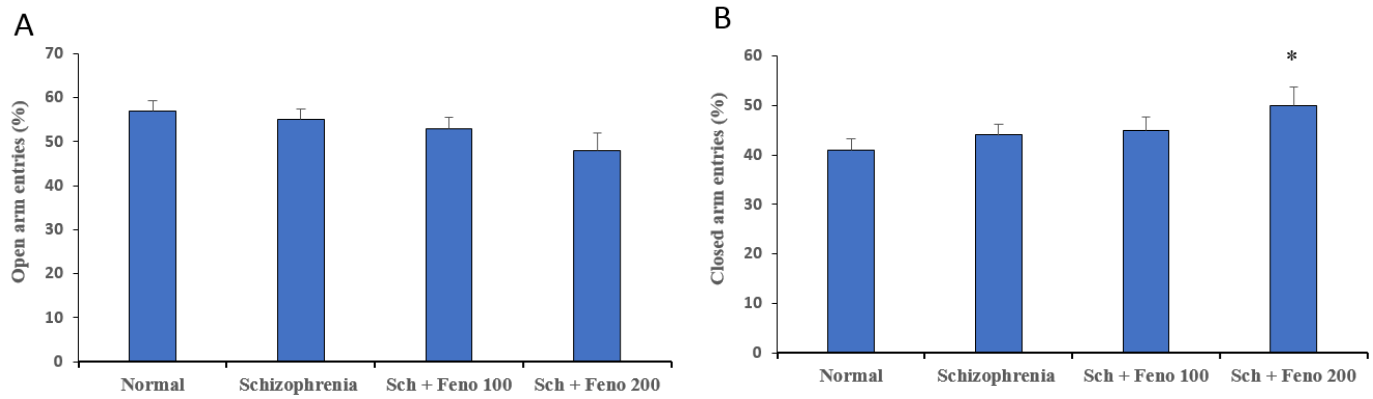


Fig 3: Effect of fenofibrate on the percentage of entries into the open arm (A) and closed arm (B) of the elevated plus-maze in a ketamine-induced animal model of schizophrenia. All data are presented as mean ± standard error of the mean (SEM). The symbol * ($p < 0.05$) indicates statistically significant differences compared with the normal control group.

Discussion

The findings of the present study demonstrated that induction of a schizophrenia-like model with ketamine significantly reduced locomotor activity. Furthermore, animals in this model exhibited marked alterations in behavioral indices during the EPM test, characterized by a reduction in the percentage of time spent in the open arms and an increase in the percentage of time spent in the closed arms. This behavioral pattern is consistent with increased avoidance of exposed environments and may reflect enhanced anxiety-like behavior in the ketamine-induced schizophrenia (18). Although fenofibrate did not significantly alter locomotor activity in the present study, it modulated anxiety-like behavioral indices in the ketamine-induced model. Notably, these effects varied according to the dose of fenofibrate, with the 100 mg/kg dose showing a more favorable pattern of changes in the time-related indices of the EPM.

Ketamine is a non-competitive NMDA receptor antagonist that is widely used in preclinical studies to induce behavioral and neurochemical alterations relevant to schizophrenia (1, 18). The NMDA receptor hypofunction hypothesis provides an important framework for understanding the pathophysiology of the disorder, as disruption of glutamatergic transmission can affect the balance between excitatory and inhibitory networks, alter neural circuit function, and influence the regulation of other neurotransmitter systems (5, 19). In the present study, behavioral alterations were evident in animals exposed to the ketamine-induced schizophrenia-like model. Specifically, locomotor activity was reduced, the percentage of time spent in the open arms decreased, and the percentage of time spent in the closed arms increased. Pellow et al. demonstrated that rodents exhibit an innate preference for closed arms and that both the time spent in and the number of entries into the open arms are associated with anxiety-related behavior (20). In classical pharmacological studies using the EPM, increased time spent in and entries into the open

arms are generally associated with reduced anxiety-like behavior, whereas reductions in these indices are typically interpreted as reflecting increased anxiety-like behavior (17). Accordingly, the reduced percentage of time spent in the open arms observed in the ketamine-treated group may indicate increased avoidance of exposed areas and enhanced anxiety-like behavior. However, this index alone is insufficient to establish a definitive alteration in anxiety-like behavior (19). Importantly, the ketamine-induced model does not fully reproduce the complexity of human schizophrenia. Behavioral responses to ketamine may vary depending on factors such as dose, duration of exposure, animal species and strain, environmental conditions, and the interval between the last administration and behavioral testing. Moreover, the consequences of NMDA receptor blockade may not manifest in the same direction across different behavioral indices (1). Therefore, the behavioral findings observed in the present study should not be interpreted as a direct representation of all clinical dimensions of schizophrenia; rather, they should be considered within the specific behavioral context of the ketamine-induced model and its inherent methodological limitations (18, 19).

Although the EPM provides information about both anxiety-like behavior and exploratory activity, arm entries may be influenced by both motor activity and anxiety-related avoidance. Therefore, changes in arm entries should not be interpreted as a direct measure of locomotor activity or anxiety in isolation. In the present study, locomotor activity was assessed separately and considered alongside the EPM measures to facilitate a more cautious interpretation of the behavioral outcomes. Nevertheless, the absence of an independent locomotor assessment, such as the Open Field Test, represents a limitation of the study. Future investigations incorporating complementary behavioral tests would help distinguish motor effects from anxiety-related behavioral changes more clearly.

One of the notable findings of the present study was the alteration in the temporal indices of the EPM in the group treated with fenofibrate, particularly at the 100 mg/kg dose. In this group, the percentage of time spent in the open arm increased, while the time spent in the closed arm decreased, bringing the pattern of these indices closer to that of the normal group. From a behavioral pharmacology perspective, this pattern is consistent with a relative reduction in avoidance of the open environment and may indicate a modulation of associated behavioral changes or the anxiety-like behavior observed in the ketamine-induced schizophrenia model (17). However, interpreting this finding as a specific anxiolytic effect of fenofibrate requires caution, as locomotor activity in the drug-treated group was also lower in a descriptive comparison with the normal group. Regarding molecular changes, fenofibrate can influence the expression of genes related to lipid metabolism, energy homeostasis, and certain cellular regulatory pathways through the activation of PPAR-α (9). Preclinical evidence has also suggested a link between this receptor and specific neurobiological processes and behavioral phenotypes associated with schizophrenia (21). Studies indicate that PPAR-α is a ligand-activated nuclear receptor that plays a role in metabolic processes and certain inflammatory responses by regulating the transcription of target genes (12). In recent years, the potential role of this receptor in nervous system function and neuropsychiatric disorders has also garnered attention. Preclinical evidence has suggested a link between the PPAR-α pathway and certain phenotypes associated with schizophrenia, indicating that activation of this receptor may influence specific neurobehavioral changes in animal models (11, 14). Quittet et al. reported that fenofibrate, acting as a PPAR-α agonist, was able to modulate prepulse inhibition (PPI) deficits in a developmental model of schizophrenia (21). The current study is significant as it demonstrates that PPAR-α activation can affect a behavioral phenotype linked to sensorimotor gating deficits in a schizophrenia model (21). Furthermore, using a model of maternal immune inflammation, De Felice et al. reported that fenofibrate could ameliorate certain behavioral abnormalities associated with the schizophrenia phenotype as well as alterations in dopamine transmission (14). These findings support the hypothesis that PPAR-α may play a role in regulating neural processes linked to schizophrenia-related phenotypes. However, direct comparisons between these studies and the present study should be made with caution, given the differences in the animal models and behavioral indices employed. From a

pathophysiological perspective, the potential link between PPAR-α and the observed behavioral changes can be examined within the framework of several interconnected pathways (15). Various models of schizophrenia have been associated with NMDA receptor dysfunction, alterations in dopamine transmission, neuroinflammation, oxidative stress, and synaptic dysfunction (5). PPAR-α is also a ligand-activated nuclear receptor involved in the regulation of lipid metabolism, inflammation, oxidative responses, and cellular homeostasis (13, 21). Therefore, PPAR-α activation by fenofibrate could theoretically influence the behavioral phenotype through the modulation of inflammation, oxidative stress, or neuronal function.

The differential behavioral response to the two fenofibrate doses is pharmacologically noteworthy. The relationship between drug dose and biological response is not necessarily linear, and increasing the dose does not invariably produce a greater behavioral effect. New evidence also underscores the importance of dose- and tissue-dependent biological responses. In a study involving rats, Pannala et al. demonstrated that fenofibrate induces dose-dependent transcriptional changes, with distinct patterns observed in the liver and kidney (22). Furthermore, the regulation of PPAR-α receptor-related pathways varied across different drug exposure conditions. These findings highlight the complexity of fenofibrate's pharmacological effects, suggesting that the intensity and nature of the biological responses it elicits may be influenced by the administered dose and the specific tissue type. Additionally, Kovalenko et al. reported that fenofibrate administration in an animal model of temporal lobe epilepsy reduced anxiety-like behaviors and improved certain indices of exploratory behavior (23). These behavioral changes were accompanied by region-specific alterations in glutamate receptor expression and markers of neuroinflammation. The study's results indicate that the behavioral effects of fenofibrate may depend on the underlying pathophysiological state and the associated neuronal and molecular responses. Therefore, the distinct behavioral patterns observed following the 100 and 200 mg/kg doses may reflect dose-specific pharmacological effects rather than a simple linear dose–response relationship. However, because the present study did not directly assess pharmacokinetic parameters, receptor engagement, or downstream molecular signaling, the mechanisms underlying the differential responses to the two doses remain speculative and warrant further investigation.

Conclusion

Based on the current findings, it can be concluded that the administration of fenofibrate at specific doses modulated certain behavioral indices associated with anxiety-like behaviors in a ketamine-induced model of schizophrenia. While this finding may support a potential role for PPAR-α in modulating specific behavioral indices in schizophrenia models, further behavioral studies and direct molecular evidence are required to validate this relationship.

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